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TIMING OF VULNERABILITY OF THE BRAIN TO IODINE DEFICIENCY IN ENDEMIC CRETINISM

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Abstract *Background.* Endemic cretinism, caused by severe iodine deficiency during pregnancy, is the world's most common preventable cause of mental retardation. It can be prevented by iodine treatment before conception, but whether it can be prevented or ameliorated by treatment during pregnancy or after delivery is not known.

Methods. In a severely iodine-deficient area of the Xinjiang region of China, we systematically administered iodine to groups of children from birth to three years of age (n=689) and women at each trimester of pregnancy (n=295); we then followed the treated children and the babies born to the treated women for two years. We used three independent measures of neural development: the results of the neurologic examination, the head circumference (which correlates with brain weight in the first postnatal year), and indexes of cognitive and motor development. Untreated children one to three years of age, who were studied when first seen, served as control subjects.

Results. The prevalence of moderate or severe neurologic abnormalities among the 120 infants whose mothers received iodine in the first or second trimester was 2 percent, as compared with 9 percent among the 752 infants who received iodine during the third trimester (through the treatment of their mothers) or after birth (P=0.008). The prevalence of microcephaly (defined as a head circumference more than 3 SD below U.S. norms) decreased from 27 percent in the untreated children to 11 percent in the treated children (P=0.006), and the mean (±SD) developmental quotient at two years of age increased (90±14, vs. 75±18 in the untreated children; P<0.001). Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but head growth and developmental quotients improved slightly. Treatment during the first trimester, which was technically problematic, improved the neurologic outcome.

Conclusions. Up to the end of the second trimester, iodine treatment protects the fetal brain from the effects of iodine deficiency. Treatment later in pregnancy or after delivery may improve brain growth and developmental achievement slightly, but it does not improve neurologic status. (N Engl J Med 1994;331:1739-44.)

SEVERE endemic iodine deficiency causes endemic cretinism, characterized by deaf-mutism, intellectual deficiency, rigid–spastic motor disorder, and sometimes hypothyroidism.[1-5] Cretinism occurs in as many as 2 to 10 percent of the population of isolated communities in many areas of the world,[5] and it is considered the world's most common preventable cause of mental retardation.[6,7] In iodine-deficient populations, a mild degree of mental impairment occurs five times as frequently as cretinism[8,9] and the IQ curve of the population can be shifted 10 points to the left.[10]

Endemic cretinism can be prevented by iodine treatment, but its pathogenesis remains obscure. Treatment of sporadic congenital hypothyroidism with thyroid hormone beginning in the neonatal period permits normal neurologic development[11]; however, iodine treatment at birth does not prevent endemic cretinism,[12] which is caused by a combination of maternal and fetal hypothyroxinemia during gestation.[13-16] The mechanism and the timing of this developmental injury have not been identified. We designed this study to clarify the time during fetal and postnatal development when iodine supplementation is effective in preventing brain damage and, conversely, the stage of development at which iodine deficiency results in brain damage that is not reversible by iodine treatment. The study was performed in an area of severe iodine deficiency; we studied the base-line situation, provided iodine to pregnant women and young children, and then followed the women's babies and the treated children over time.

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METHODS

Hotien Prefecture in Xinjiang–Uighur Autonomous Region, People's Republic of China (population, 1.2 million), is an area of severe iodine deficiency in which adequate iodine intake has not been achieved and in which cretinism occurs frequently. The concentrations of iodine in the water and soil are among the lowest ever recorded. The area is in the Takla Makan Desert on an alluvial plain near the Kunlun Mountains.

This study was carried out during the period 1990 through 1994 by a joint Chinese–Uighur–U.S. team in eight villages (each of about 300 families) in Tusala township (population, 31,000), located 6 km from the city of Hotien in the Karakax River plain. Severe iodine deficiency has long been recognized in this region; 2 percent of the people had cretinism and 54 percent had visible goiter in a 1990 survey; the median urinary iodine excretion is 10 to 25 μg per liter (0.08 to 0.2 μmol per liter), the iodine content in water is 1.2 μg per liter (0.01 μmol per liter), and that in soil is 7 to 240 μg per kilogram (0.06 to 1.9 μmol per kilogram) (unpublished data). The people are Uighurs, of Turkic origin, who live as subsistence farmers. The annual family income ranges from $70 to $250 (U.S.). The annual birth rate is 2.2 percent (based on village records). Infant mortality is high, protein-energy malnutrition is nearly universal in young children, and rickets is common.

Previous systematic iodine-treatment programs, including those using iodized salt, intramuscular injections of iodinated oil (in 1984), and the oral administration of iodinated oil (in 1988), have not been effective in preventing iodine deficiency on a long-term basis in this region. No records of these programs exist, but retrospective questioning indicated that few women of childbearing age had received iodine. In any event, the effect would have dissipated before 1990 because oral iodinated oil provides protection only for 6 to 18 months.[17]

Study Design

This study was designed to determine whether the treatment of newborn infants, young children, and pregnant women (and their fetuses) with iodine at different ages and during different trimesters of pregnancy would improve neurologic and mental development, as compared with the development of cohorts of older children who had not previously received iodine supplementation. The study was approved by the institutional review board of Duke University. All the parents gave oral informed consent: a Uighur-speaking physician was part of the team at all times.

The study subjects were 689 children (169 from 2 to 3 years old, 171 from 1 to 2 years old, 170 from 3 to 12 months old, and 179 newborns less than 3 months old) and 295 pregnant women (48 in the first trimester, defined as more than six months before delivery; 99 in the second trimester, defined as three to six months before delivery; and 148 in the third trimester, defined as three months or less before delivery). Two sets of twins were born to women treated during pregnancy. There was no specific provision for a group of women to receive iodine before conception, but during the course of the study it was found that this had occurred in the cases of 13 women. Nearly all eligible children and women in the eight study villages participated; there was no evidence to suggest any systematic selection bias. The interval from iodine treatment until delivery was used to define the trimester of treatment. Approximately equal numbers of pregnant women were given oral iodine treatment at one of two specific times, June and November, in order to balance any seasonal effect.

The 689 children, their mothers, and the 295 pregnant women were treated with oral iodinated oil (400 mg of iodine for adults, 50 mg for children up to 12 months of age, and 200 mg for older children) at the time of their first encounter with the study physicians; all the subjects were treated again at six-month or annual reevaluations, including those first treated in utero. Iodinated oil was used until late 1991, when the treatment was changed because the government began to supply tablets containing 0.1 mg of potassium iodide, one of which was to be taken daily for four days each year; this change had a critical effect only for women treated during the first trimester, who were the last group to be enrolled. Cohorts of infants whose mothers received iodine during the first, second, or third trimesters were compared; they were also compared with groups of children up to three years of age who were examined before treatment; these children served as control subjects. There were no untreated control groups.

In preliminary studies, 30 children 2 to 14 years of age with clinically diagnosed cretinism were examined to determine the characteristics of the disorder in this region. In this study those with the most severe motor disability had the most severe microcephaly. The 3 children with quadriplegia had head-circumference values 9, 4.7, and 4.3 SD below the U.S. norms; the 13 children with severe cretinism who were able to walk had a mean head circumference 3.1 SD below the norm; 8 other children who had hypotonia or ataxia had a mean head circumference 2.1 SD below the norm; and the 6 mildly affected children were normocephalic.

Urinary iodine excretion (measured in random samples) and serum thyroxine and thyrotropin concentrations were measured in the pregnant women before treatment. Urinary iodine excretion and serum thyroxine concentrations decreased and serum thyrotropin concentrations increased during the course of pregnancy. These findings replicate others in iodine-deficient populations[18] and suggest that the transfer of iodine to the fetus puts increasing stress on maternal pituitary–thyroid function.

Clinical, Neurologic, and Developmental Examinations

The children were evaluated every six months or every year with measurements of height, weight, and head circumference; physical and neurologic examinations; assessments of the attainment of developmental milestones; and measurements of serum thyroxine and thyrotropin and urinary iodine excretion. The examinations were performed by team physicians, two of whom were Uighur; each became skilled at one part of the examination. In any age group, not all children had all examinations performed; thus, the numbers of subjects in each group for whom results are reported differ among the variables.

The neurologic examinations, recorded on age-appropriate standardized forms in Chinese, included assessments of hearing, vision, social responsiveness, extraocular movements, muscle tone, reflexes, motor strength, gross- and fine-motor skills, vocalization, and stance and gait. The children were classified as having moderate or severe abnormalities (definite abnormalities of muscle tone, reflexes, ability to sit or stand, gait, hand use, extraocular movements, vision, hearing, or responsiveness), having mild abnormalities (no definite abnormalities, but a delay in the attainment of milestones or decreased activity), or normal. The assessments were made independently by the same two physicians throughout the study; differences were reconciled by joint review of the records. The examiners were aware of the patients' treatment status but did not know, in general, the time of treatment.

Measurements of Head Circumference

Head circumference can be easily and precisely measured and correlates with brain growth (between 33 and 44 cm, head circumference correlates nearly linearly with brain weight[19]) and the mid-childhood intelligence quotient.[20] We normalized the head-circumference data for age and sex by calculating standard deviations from the mean (z score) as the index variable, using U.S. norms.[21] In the Tusala population, the mean head circumference of young children deviates increasingly below U.S. norms with increasing age, making it essential to compare groups of children at the same ages. Standard deviations for head-circumference values were plotted against age; semilogarithmic regression curves (using the natural logarithm of age) were empirically fitted to the data. Student's t-test was used to compare the means for different groups at the same age. Head-circumference data for the treated newborns were compared with neurologic status in the newborn period (birth to three months) and at one year of age. The prevalence of microcephaly (defined as a head circumference more than 3 SD below the U.S. mean at 12 to 22 months) was calculated for each group.

Developmental Testing

Developmental quotients were derived from individual assessments when the children were about 24 months of age; these consisted of developmental tasks in four subject areas: fine-motor skills, gross-motor skills, cognitive development, and language skills. Test items were taken from the Bayley Scales of Infant Development (1969 edition).[22] In each subject area, items within 6 months above and below the 24-month level were used; that is, the assessment included developmental milestones from 18 to 30 months of age. The test items and materials were attractive, colorful, and not specific to any culture, and the assessment was brief (10 to 15 minutes). After field testing in Hotien, inappropriate items were deleted. The most advanced tasks the child was able to perform successfully in each area were used to calculate an average developmental age, and a ratio was derived (developmental age ÷ chronological age × 100) as an index of overall development. U.S. norms were used for scoring.

RESULTS

Mortality

Follow-up information was obtained for 89 percent of the infants given iodine in the postnatal study and for 96 percent of the infants whose mothers received iodine

Table 1. Outcomes of Pregnancies in Women Treated with Iodine, According to the Timing of Treatment.

Outcome	Before Conception	First Trimester	Second Trimester	Third Trimester: Early	Third Trimester: Late
	no. of pregnancies				
Total	13	48	99	148	
Abortion	1	6	1	2	
Fetal death	3	10	6	7	
Not pregnant or lost to follow-up*	0	4	0	2	
Treated	9	28	92	74	63
	no. of infants (%)				
Abnormality†					
Mild	0 (0)	4 (14)	3 (3)	4 (5)	10 (16)
Moderate or severe	0 (0)	0 (0)	2 (2)	4 (5)	4 (6)

*Indicates women originally enrolled who later proved not to be pregnant or were lost to follow-up.

†Mild and moderate or severe abnormalities were by definition those in children with abnormal neurologic status.

during pregnancy; the data included fetal loss and postnatal mortality (Table 1). The rates of fetal loss and misdiagnosis of pregnancy were higher among the women treated in the first trimester. Fetal or neonatal mortality did not differ significantly in the second- and third-trimester groups.

Neurologic Findings

The neurologic findings in each study group are shown in Figure 1. The untreated two-to-three-year-olds and the one-to-two-year-olds (i.e., those who were evaluated before treatment) served as historical controls. Iodine treatment at 3 to 12 months of age, during the neonatal period (birth to 3 months), or during the third trimester had no effect on neurologic outcome as assessed at one to two years of age. There was no difference in the prevalence of moderate or severe abnormalities in the infants treated early in the third trimester (3 to 1.5 months before delivery) and those treated late in that trimester (less than 1.5 months before delivery), but mild abnormalities were less frequent in those treated early in the third trimester. Iodine treatment during the second or first trimester was associated with a substantially better neurologic outcome at the age of one to two years, as compared with the outcome in untreated infants of the same age. Among the 120 infants whose mothers were treated in the first or second trimester, the prevalence of moderate or severe neurologic abnormalities was 2 percent, as compared with 9 percent (P = 0.008) among the 752 infants treated in the third trimester or after delivery.

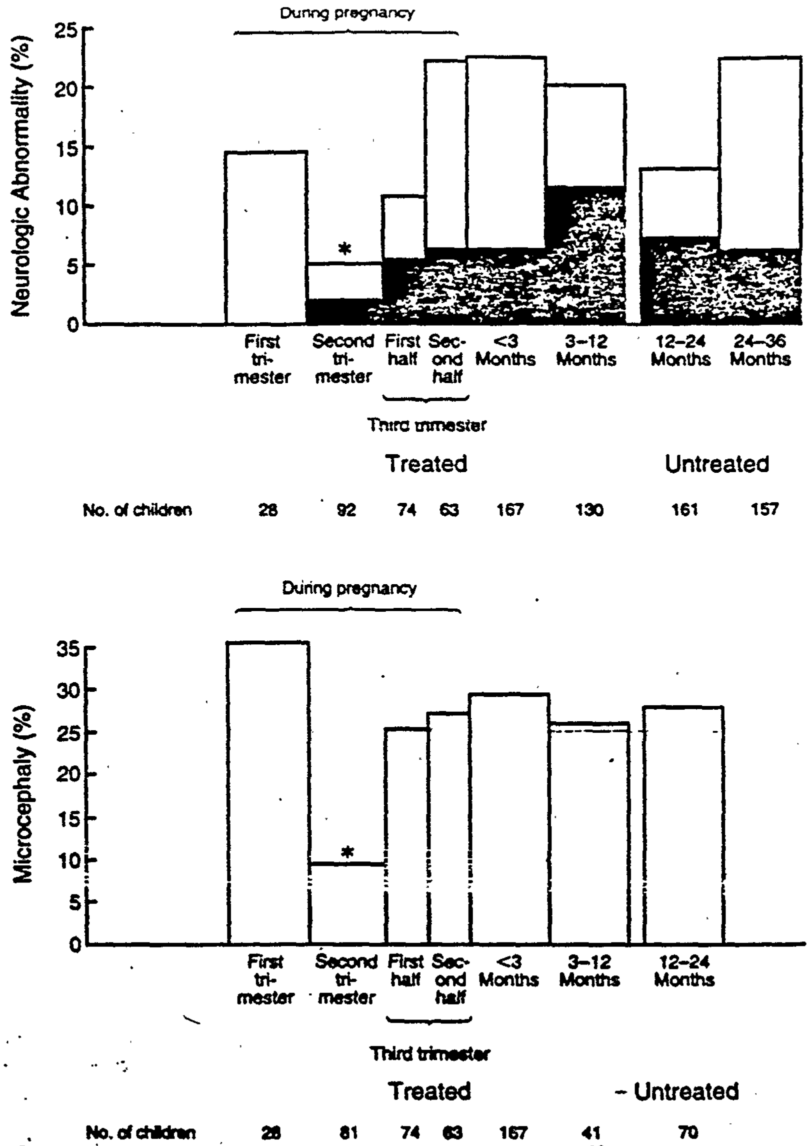

Figure 1. Rates of Neurologic Abnormality and Microcephaly at 1 to 2 Years of Age in Untreated Children and in Children Treated with Iodine Prenatally or up to 1 Year after Birth and Rates of Neurologic Abnormality in Untreated Children 24 to 36 Months of Age.

In the upper panel, the solid bars indicate moderate or severe neurologic abnormalities, and the open bars mild neurologic abnormalities. The asterisk indicates P<0.001 for the comparison with children treated later and untreated children. In the lower panel, microcephaly is defined as a head circumference more than 3 SD below the U.S. mean at 12 to 22 months of age. The asterisk indicates P = 0.006 for the comparison with children treated later and untreated children. The numbers below the panels indicate the number of children in each group.

Head Circumference

Among untreated newborns, the mean head circumference was significantly smaller in neurologically abnormal infants (Fig. 2). This difference increased despite treatment during the first postnatal year in the infants with moderate or severe neurologic abnormalities. In previously untreated infants who were first examined at one to three years of age, the values for median head circumference were lower and the prevalence of microcephaly was 25 to 28 percent. Children whose mothers were treated during the third trimester of pregnancy or after delivery had no greater head growth than untreated children up to 12 months of age, but thereafter they appeared to have moderately greater growth. Children treated during the second trimester had a statistically significant increase in head circumference as compared with the untreated children; their median head circumference was larger (1.4 SD below the U.S. mean, P<0.001), and the prevalence of microcephaly was lower (11 percent, vs. 27 percent in those treated later; P = 0.006). The results for the children whose mothers were treated during the first trimester are discussed below.

Assessments of Developmental Milestones

Altogether, 404 children had developmental testing at about two years of age (Table 2). The group whose mothers received iodine during the second trimester of pregnancy, including 18 children whose mothers were treated six months before delivery, had a mean (±SD) developmental score that was significantly higher than that in the untreated group (90±14 vs. 75±18). The group whose mothers received iodine during the third trimester, the group treated as newborns, and the group treated at 3 to 12 months had slightly higher scores than the untreated group (P=0.06 to 0.10). The group whose mothers were treated during the first trimester had a mean score similar to that of the untreated group. The developmental test results were not affected by the sex of the child, the mother's age at delivery, or the presence of goiter in the mother.

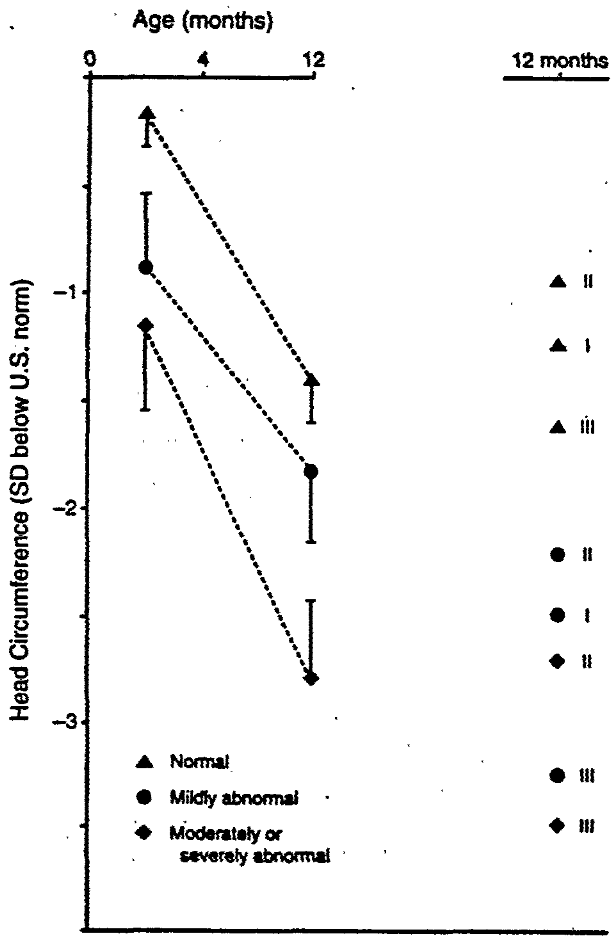

Figure 2. Mean Head Circumference of Infants Rated Neurologically Normal (130 Children), Mildly Abnormal (26 Children), or Moderately or Severely Abnormal (11 Children) When Examined as Newborns (Birth to 3 Months of Age) and at 12 Months of Age. All the infants received iodine at the time of the first examination. The mean head circumference of the normal infants was significantly larger at both ages than that of the infants with abnormalities (P=0.005). The right-hand column shows the mean head circumference at 12 months of age among children whose mothers were treated during the first (I), second (II), and third (III) trimesters of pregnancy and who were neurologically normal, mildly abnormal, or moderately or severely abnormal. Here also the mean head circumference of the normal infants was significantly larger than that of the infants with abnormalities (P=0.005).

Table 2. Results of Developmental Testing at Two Years of Age among Untreated Children and Children Treated with Iodine before Two Years of Age.

Timing of Treatment	Developmental Quotient*	No. of Children	P Value†
	mean ±SD		
Treated during pregnancy	83±14	184	0.007
First trimester	77±11	28	0.5
Second trimester	90±14	71	<0.001
Third trimester	80±15	85	0.08
Treated as newborns (birth to 3 mo)	79±10	90	0.10
Treated 3–12 mo after delivery	80±8	93	0.06
Untreated (2-year-olds)	75±18	37	—
Total	—	404	—

*By comparison with U.S. norms (mean [±SD], 100±16).

†For the comparison of each group at 24 months with the untreated group, by Student's t-test.

Children of Mothers Treated during the First Trimester

The group of children whose mothers were treated during the first trimester of pregnancy (more than six months before delivery) was the last recruited, because special efforts were necessary to identify women in early pregnancy, including the use of urine pregnancy tests. Women were also sought in adjoining towns similar to Tusala. All these women were treated with potassium iodide tablets, which contained only a small amount of potassium iodide (0.1 mg), to be taken once daily for four days; data on compliance and the duration of effectiveness are lacking. As compared with the 18 children born to mothers who were treated six months before delivery (10 with tablets), the children whose mothers were treated earlier had a smaller mean head circumference, lower mean developmental quotient, and smaller stature (Table 3). Four of those 28 children had mild neurologic abnormalities, as compared with none of the group treated at six months.

Discussion

We have shown that the administration of iodine to pregnant women during the second trimester of pregnancy improved neurologic and psychological development in their children, as indicated by three independent measures of development at two years of age; the children treated prenatally had fewer neurologic abnormalities, increased head growth, and an improved developmental quotient. Treatment after the beginning of the third trimester was not associated with improvement in neurologic status, but head growth after one year of age and developmental quotients may have improved somewhat. These results suggest that iodine de-

Table 3. Results in Children Whose Mothers Received Iodine Six Months or More before Delivery.*

Time of Treatment (mo before delivery)	No.	Head Circumference	DQ	Height	No. with Mild Neurologic Abnormality
6 (included in second trimester)	18	−1.5±1.1	88±8	−2.5±0.8	0
>6–7	10	−1.9±1.2	77±9	−3.5±0.8	1
>7–8	10	−2.8±1.3	76±11	−2.6±0.9	1
>8–9	8	−2.6±1.4	77±16	−3.7±2.3	2
P value (6 vs. >6–9 mo)	—	0.02†	<0.001†	0.04†	0.20‡

*Head circumference and height are expressed in standard deviations from the U.S. mean for children of the same age. DQ denotes developmental quotient. For neurologic abnormalities, the number with mild abnormality is shown; none of these children had moderate or severe abnormality.

†By Student's t-test.

‡By the chi-square test.

ficiency at the beginning of the third trimester causes irreversible abnormalities in head growth and neurologic development. Although it did not improve neurologic development, treatment during the third trimester or during the newborn period was associated with a trend toward higher developmental scores (as compared with those in untreated infants) and a slightly larger mean head circumference after one year of age. Thus, the effect of treatment on these measures may last longer (through the first postnatal year) than its effects on earlier head circumference and neurologic status.

The women treated during the first trimester of pregnancy received an inadequate amount of iodine, because of the change in the form of supplementation from iodinated oil to oral tablets. One tablet, containing 0.1 mg of potassium iodide, was to be taken daily for four days; these were often not taken under supervision. The change to a lower, unsupervised dose explains the finding that treatment during the first trimester was associated with poorer outcomes in the children; outcomes were worse the earlier treatment was given. This inadequate treatment appears to have had a favorable effect on neuromotor development, but not on later brain growth or developmental scores.

On the basis of experimental studies it appears that thyroxine primarily affects neuronal differentiation, the formation of neural processes, and synaptogenesis.[23,24] In human fetuses, the proliferation of neurons for the cerebral cortex, cochlea, and basal ganglia (structures implicated in the deficits that characterize cretinism[4,5,25]) occurs mostly during the second trimester. The increase in brain weight and protein content, correlating with cell differentiation, is most rapid during the third trimester.[26] Thus, iodine deficiency in the third trimester could explain postnatal microcephaly. A critical event early in the third trimester also appears to limit later brain growth, since later treatment caused only slight and delayed catch-up increases in head circumference. In summary, a thyroxine-dependent event, important for subsequent brain growth and neuromotor development, may occur during a fairly narrow period at the beginning of the third trimester. Interestingly, treatment with iodine during the third trimester or the neonatal period appears to cause increased head growth that begins only after one year of age (Fig. 3); this suggests that a second critical thyroxine-dependent event in the newborn period may determine brain growth that becomes evident only much later and that this event is therefore important for mental development.

In iodine-deficient sheep fetuses treated with iodine or thyroxine at the end of the second trimester (100 days), histologic examination of the brain at 140 days showed overall improvement after treatment, but some defects, including impaired synaptogenesis, were not corrected.[27] In a study in which women received injections of iodized oil, cretinism was prevented by injections before conception but not thereafter,[3] leading to the conclusion that iodine deficiency has crucial effects in the first trimester of pregnancy. In that study, among 90 women treated during pregnancy, the children of 5 had cretinism; 4 of the mothers were treated at approximately 26, 30, 32, and 36 weeks of gestation and 1 at approximately 13 weeks. Fetal ages were esti-

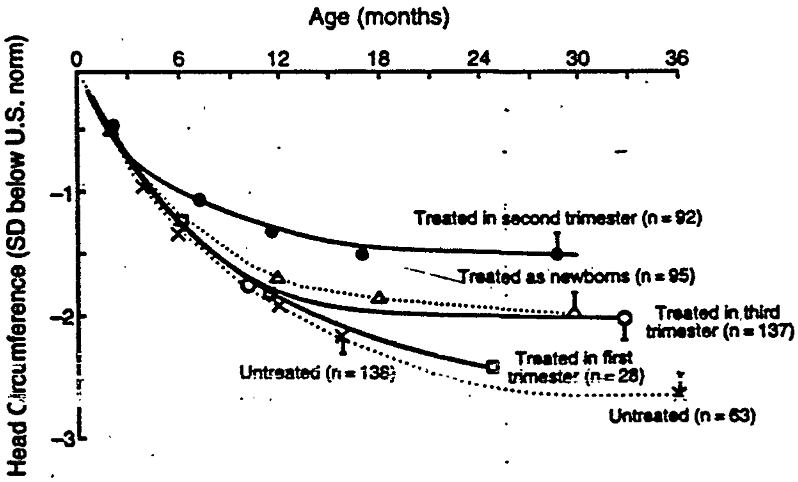

Figure 3. Mean Growth in Head Circumference among Untreated Children and among Children Treated with Iodine, According to Time of Treatment.

The groups include children treated during the newborn period (those less than three months of age) and those whose mothers were treated during the first, second, or third trimester of pregnancy. Mean head circumference is expressed as the number of standard deviations (z score) below the U.S. norm.[21] The curves are semilogarithmic regression curves that best fit the data (SD for head circumference vs. the natural log of postnatal age in months). The bars show the standard errors of the mean values. The numbers given for the untreated children represent different groups assessed at different ages.

mated retrospectively and were imprecise, since in this population exact birth dates were not noted. These results do not contradict ours; treatment during the third trimester was not protective, and only one case of cretinism resulted after apparently timely treatment (at 13 weeks). Some have expressed concern about possible harm to the fetus from transient hypothyroidism after treatment with large doses of iodine late in the third trimester.[28] Our results do not suggest such a problem.

Our findings have practical implications for iodine prophylaxis. It is obviously preferable to start providing iodine before pregnancy and to provide it continually. In Hotien, for example, we developed a technique of adding potassium iodate to irrigation water to provide iodine on an ongoing basis to the entire population.[29]

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